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Research Paper

# Is an Early Age at Illness Onset in Schizophrenia Associated With Increased Genetic Susceptibility? Analysis of Data From the Nationwide Danish Twin Register

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ABSTRACT

*Background:* Early age at illness onset has been viewed as an important liability marker for schizophrenia, which may be associated with an increased genetic vulnerability. A twin approach can be valuable, because it allows for the investigation of specific illness markers in individuals with a shared genetic background.
*Methods:* We linked nationwide registers to identify a cohort of twin pairs born in Denmark from 1951 to 2000 ($N = 31{,}524$ pairs), where one or both twins had a diagnosis in the schizophrenia spectrum. We defined two groups consisting of; $N = 788$ twin pairs (affected with schizophrenia spectrum) and a subsample of $N = 448$ (affected with schizophrenia). Survival analysis was applied to investigate the effect of age at illness onset.
*Findings:* We found that early age at illness onset compared to later onset in the first diagnosed twin can be considered a major risk factor for developing schizophrenia in the second twin. Additionally, we found that the stronger genetic component in MZ twins compared to DZ twins is manifested in the proximity of assigned diagnosis within pairs.
*Discussion:* Early onset schizophrenia could be linked to a more severe genetic predisposition, indicating that age might be perceived as a clinical marker for genetic vulnerability for the illness.


## 1. Introduction

Age at onset has been proposed as the most important characteristic of schizophrenia that provides knowledge about the origin of the disorder (DeLisi, 1992). Studies have reported early age at illness onset to be characterized by a worse course of illness, with more positive family history of psychosis and an increased risk of illness in siblings (Rabinowitz et al., 2006; Byrne, 2002; Hosmer et al., 2008; Husted et al., 2006). Therefore it can be viewed as a distinct phenotypic liability marker for schizophrenia because it may represent a specific subtype of the disorder (Goldberg et al., 2011). The risk of developing schizophrenia has consistently been reported higher in males (Aleman et al., 2003), while the peak in age at onset is equal between sexes at around age 22, with a difference in the mean age at onset being later for females (Pedersen et al., 2014; van der Werf et al., 2014; Thorup et al., 2007). This underlines the importance of addressing possible sex differences when studying illness vulnerability. In this regard, a meta-analysis found that the presence of a family history of psychosis influenced an earlier age at onset in both sexes compared to families without a history of psychosis in which only the male sex was associated with early illness onset (Esterberg et al., 2010). A recent study focused on illness course and did not find an association between gender and age at onset on the course of illness when adjusting for symptom severity at illness presentation, indicating that these features offer little prognostic value (Drake et al., 2016). This suggests that early age at illness onset might be a relevant clinical marker for increased genetic vulnerability in which sex may be a modifying factor, rather than a marker for symptom severity and illness course.

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Exposure to specific environmental factors increases the risk to develop schizophrenia in vulnerable individuals (van Os et al., 2010), thus environmental and genetic factors may both influence age at illness onset in schizophrenia. Accumulated exposures such as obstetric complications, trauma, urbanicity and cannabis use seem to have a major impact on lowering age at onset in male patients (Stepniak et al., 2014). A Swedish register-based study combined the study of environmental and genetic risk, by measuring sibling risk of schizophrenia both in affected and unaffected families and described an increased risk in siblings in affected families compared to unaffected families. The risk was modified by factors like higher age at onset in probands, advanced paternal age and immigrant status of parents (Svensson et al., 2012). These findings support a role for environmental risk factors in age at schizophrenia onset. Specific genetic polymorphisms are also associated with early age of schizophrenia onset, although only present in male patients (Hänninen et al., 2007; Yuan et al., 2013). A GWAS study could not draw significant conclusions regarding genetic association with age at onset, severity of disorder or disease associations by family history of schizophrenia and sex (Bergen et al., 2014); however, a more recent study identified a correlation between specific genetic variations and a lower age at schizophrenia onset (Chow et al., 2016). In conclusion, there is a lack of evidence for a simple genetic association between the timing of illness onset and sex or family history, or to what extent genetic risk affects age of illness onset in both sexes.

In general, twin studies allow for the study of phenotypic, endophenotypic and biological discordance in individuals with a shared genetic background, which makes it a valuable tool in studying complex human traits and disorders such as schizophrenia. The classic twin study compares phenotypic resemblances of monozygotic (MZ) and dizygotic (DZ) twins to identify genetic variation in disease susceptibility (Boomsma et al., 2002). A twin design can examine "age at illness onset" as a specific liability marker of schizophrenia, in relation to the genetic impact on disease liability, and furthermore investigate possible sex differences.

This study aims to examine age at illness onset and risk of schizophrenia and schizophrenia spectrum disorders in a national twin cohort identified in the Danish Twin Register using information from the Danish Psychiatric Central Research Register. In the study we will focus on two diagnostic categories; a narrow definition of schizophrenia as outlined in ICD-8 and ICD-10, and a broader phenotypic outcome representing the schizophrenia spectrum in ICD-8 and ICD-10. Specifically, we will investigate if an early onset of schizophrenia and schizophrenia spectrum in the first diagnosed twin (<22 years of age) increases the risk of illness in the second twin. In addition, we examine the importance of genetic effects in the timing of illness onset in twin pairs by testing whether the higher genetic similarity in MZ twins compared to DZ twins is associated with closer proximity of assignment of diagnoses in the twin pairs.

## 2. Methods

The study is approved by the Danish Data Protection Agency and the Danish National Board of Health.

### 2.1. National Registers

The present sample is based on linkage of two nationwide registers, the Danish Twin Register and the Danish Psychiatric Research Register, thereby identifying a sample of twin pairs born 1951–2000. At birth all individuals are registered with a unique identification number in the Danish Central Civil Registration System, and using this register it is possible to identify all individuals across registers (Pedersen et al., 2006). The Danish Twin Register includes twin pairs born in Denmark from 1870 onwards, it was initiated in 1954 and the ascertainment of live-born twin pairs is complete from 1968 (Skytthe et al., 2011). Zygosity information is not available from all twins in the register (Skytthe et al., 2011). Twins with unknown zygosity (UZ) are removed from the sample, since our aim is to investigate the genetic predisposition in relation to early illness onset, and in UZ twins the degree of shared genetic material is unknown. The Danish Psychiatric Central Case Register contains information on all admissions to a psychiatric facility in Denmark; it was initiated in 1938, computerized in 1969 and from 1995 outpatient contacts were included in the register (Mors et al., 2011).

### 2.2. Disease Classifications

From 1969 to 1993 the ICD-8 classification system was used while the ICD-10 was used from 1994 onwards (World Health Organization, 1967, 1992). For this study schizophrenia was defined as a main or secondary lifetime diagnosis in the following ICD versions (ICD-10: F20.xx and ICD-8: 295 (excluding 295.79, schizoaffective disorder)) and schizophrenia spectrum was defined as a main or secondary lifetime diagnosis in (ICD-10: F2x.xx and ICD-8: 295, 297, 29829, 29839, 29889, 29899, 29905, 29909, 30109, 30129). We defined a lifetime diagnosis as a diagnosis received at any time during the planned observation period, in this study, from birth until June 1st, 2011. Specifically this is defined as the first date of diagnosis of schizophrenia, thus ignoring a possible diagnosis in the schizophrenia spectrum before this date. For schizophrenia spectrum it is the first date of diagnosis.

### 2.3. Statistical Analysis

Survival analysis (i.e. Cox proportional hazard modeling) was applied to investigate the effect of age at onset (below/above age 22) of the first diagnosed twin on illness outcome in the second twin (Hosmer et al., 2008). The cut-off point at age 22 is based on the peak in incidence rates at this age (Thorup et al., 2007; van der Werf et al., 2014) and a study that validated two distinct illness subtypes with an onset before and after age 22 when observing the distribution of age at onset in a large clinical sample of patients with schizophrenia (Panariello et al., 2010). To examine a possible association of increased risk of illness with decreasing age intervals we further divided the age at onset in the first diagnosed twin into 4 categories; <18, [18–22), [22 − 30) and [30, onwards). Survival analysis was also applied investigating the age intervals. Each co-twin was followed from birth until date of schizophrenia, censoring or death. By estimating zygosity-specific Kaplan-Meier curves for the affected twin pairs we aim to investigate if the proximity between age at onset in twin pairs mirrors the higher genetic similarity among MZ pairs compared to DZ pairs. Data analyses were carried out using Stata version 13. The models were all adjusted for zygosity and sex to minimize bias.

### 2.4. Role of the Funding Source

The study sponsor had no role in study design, data analysis, data interpretation or writing of the paper.

## 3. Results

All individuals were followed from the computerization of the Danish Psychiatric Central Research Register in 1969 until June 1st, 2011. The present dataset contains MZ and DZ twin pairs born in Denmark from 1951 to 2000, $N = 31{,}524$ pairs. Of these $N = 788$ pairs (842 individuals) were affected with schizophrenia spectrum disorder and a subsample of $N = 448$ pairs (472 individuals) were affected with schizophrenia. The sample characteristics are described in Table 1. As mentioned in method section all UZ twin pairs have been removed in the final sample of $N = 31{,}524$ twin pairs. This includes $N = 138$ UZ pairs (157 individuals) affected with schizophrenia spectrum and a subsample of $N = 76$ UZ pairs (88 individuals) affected with schizophrenia.

Fig. 1 displays the distribution of age at onset among all twins affected with schizophrenia and schizophrenia spectrum. We observed that

**Table 1**
Frequencies (percentage) describing the two samples of affected twin pairs with schizophrenia ($N = 448$) and schizophrenia spectrum ($N = 788$) respectively.

| | Schizophrenia ($N = 448$) | | Schizophrenia spectrum ($N = 788$) | |
|---|---|---|---|---|
| | MZ ($N = 81$ pairs) | DZ ($N = 368$) | MZ ($N = 158$ pairs) | DZ ($N = 631$ pairs) |
| Concordant pairs | 12 (14.81) | 12 (3.26) | 23 (14.56) | 31 (4.91) |
| Discordant pairs | 69 (85.19) | 355 (96.47) | 135 (85.44) | 599 (94.93) |
| No. of individuals | | | | |
| Males | 82 (50.61) | 400 (54.35) | 170 (53.80) | 652 (51.66) |
| Females | 80 (49.38) | 334 (45.38) | 146 (46.20) | 608 (48.18) |
| Schizophrenia ($N = 447$)[a] | MZ ($N = 81$ pairs) | | DZ ($N = 367$ pairs) | |
| Age at onset of first diagnosed twin | SZ absent in second twin | SZ in second twin | SZ absent in second twin | SZ in second twin |
| <18 | 4 (4.94) | 0 (0.00) | 25 (6.81) | 2 (0.54) |
| [18–22) | 10 (12.35) | 4 (4.94) | 61 (16.62) | 5 (1.36) |
| [22–30) | 22 (27.16) | 6 (7.41) | 129 (35.15) | 2 (0.54) |
| ≥30 | 33 (40.74) | 1 (1.23) | 140 (38.15) | 3 (0.82) |
| Schizophrenia spectrum ($N = 787$)[b] | MZ ($N = 158$ pairs) | | DZ ($N = 630$ pairs) | |
| Age at onset of first diagnosed twin | SZ absent in second twin | SZ in second twin | SZ absent in second twin | SZ in second twin |
| <18 | 11 (6.96) | 3 (1.90) | 53 (8.41) | 5 (0.79) |
| [18–22) | 15 (9.49) | 5 (3.16) | 107 (16.98) | 10 (1.59) |
| [22–30) | 42 (26.58) | 10 (6.33) | 190 (30.16) | 8 (1.27) |
| ≥30 | 67 (42.41) | 4 (2.53) | 249 (39.52) | 8 (1.27) |

[a] $N = 487$, one pair is excluded since the diagnosis was assigned at the same day.
[b] $N = 787$, one pair is excluded since the diagnosis was assigned at the same day.

the age range is wider for the schizophrenia spectrum compared to schizophrenia and that spectrum disorders appear to have a slightly earlier onset than the narrow illness definition.

The risk of developing schizophrenia in the second twin is 4.7 times higher if the first twin has an early onset of schizophrenia, Table 2a; Hazard ratio (HR) = 4.7, 95% CI = (2.05–10.1). The risk is 4.4 times higher in schizophrenia spectrum (HR = 4.39, 95% CI = (2.56–7.52)). When adding a correction for sex in the second twin no significant change in the effect of zygosity and age at onset was observed for the risk of either schizophrenia or schizophrenia spectrum (Table 2b). The risk of both illness categories was slightly higher in women than in men but not significant (Table 2b). In addition an interaction term between sex in the second twin and age at onset was added to the model. It has no effect on the risk of schizophrenia spectrum disorder but did reduce the main effect of age at onset on risk of schizophrenia (Table 2c). A putative link between sex in the second twin and onset of schizophrenia (but not schizophrenia spectrum) is also seen when female and male twins are analyzed separately. We observed that the effect of early onset in the first twin on risk of disease in the second twin is markedly larger in females than in males. The effect is significant but there is uncertainty about the size of the effect because of wide confidence intervals (Females: HR = 8·66, CI = (2.65–28.33)) (Table 3). One pair was excluded because the twins were diagnosed on the same day, hence the final analyses included a sample of $N = 447$ and $N = 787$ pairs for analysis in schizophrenia and schizophrenia spectrum respectively. The total follow-up time in co-twins was 18,385.36 and 32,382.19 years for schizophrenia and schizophrenia spectrum respectively; this corresponds to 41.13 and 41.14 years per co-twin.

Dividing the age at onset in the first diagnosed twin into four intervals; i.e. <18, [18–22), [22–30) and [30, onwards) shows that co-twins


**Fig. 1.** Age at onset among all twins affected with schizophrenia ($N = 448$) and schizophrenia spectrum ($N = 788$) in twin pairs born 1951–2000 and identified by linkage of the Danish Twin Register and the Danish Psychiatric Central Research Register.

**Table 2**
The risk (hazard ratio (HR)) associated with developing schizophrenia/schizophrenia spectrum in the second twin if the first twin had onset of schizophrenia ($N = 447$ pairs)/schizophrenia spectrum ($N = 787$ pairs) before age 22 in a national cohort of 31,524 twin pairs born 1951–2000 and identified by linkage of Danish Twin Register and the Danish Psychiatric Central Research Register. One pair is excluded because the two twins are diagnosed on the same day. (a) HR associated with schizophrenia/schizophrenia spectrum in the second twin predicted by age at onset in the first diagnosed twin, adjusted for zygosity. (b) HR associated with schizophrenia/schizophrenia spectrum in the second twin predicted by age at onset in the first diagnosed twin, adjusted for zygosity and sex. (c) HR associated with schizophrenia/schizophrenia spectrum in the second twin predicted by age at onset in the first diagnosed twin, adjusted for zygosity with an interaction between sex and age at onset is added.

| | Schizophrenia ($N = 447$) | | | | Schizophrenia spectrum ($N = 787$) | | | |
|---|---|---|---|---|---|---|---|---|
| | HR | Std. error | *P*-value | 95% CI | HR | Std. error | *P*-value | 95% CI |
| a | | | | | | | | |
| Age of onset ≥ 22 | Reference | – | – | – | Reference | – | – | – |
| Age of onset < 22 | 4.69 | 1.98 | <0.001 | 2.05–10.74 | 4.39 | 1.21 | <0.001 | 2.56–7.52 |
| Dizygotic | Reference | – | – | – | Reference | – | – | – |
| Monozygotic | 5.65 | 2.39 | <0.001 | 2.46–12.95 | 4.19 | 1.21 | <0.001 | 2.38–7.38 |
| b | | | | | | | | |
| Age of onset ≥ 22 | Reference | – | – | – | Reference | – | – | – |
| Age of onset < 22 | 4.80 | 2.04 | <0.001 | 2.08–11.02 | 4.40 | 1.21 | <0.001 | 2.57–7.55 |
| Dizygotic | Reference | – | – | – | Reference | – | – | – |
| Monozygotic | 5.65 | 2.40 | <0.001 | 2.46–12.97 | 4.20 | 1.21 | <0.001 | 2.38–7.40 |
| Male | Reference | – | – | – | Reference | – | – | – |
| Female | 1.29 | 0.54 | n.s. | 0.57–2.94 | 1·52 | 0.43 | n.s. | 0.88–2.63 |
| c | | | | | | | | |
| Age of onset ≥ 22 | Reference | – | – | – | Reference | – | – | – |
| Age of onset < 22 | 2.51 | 1.58 | n.s. | 0.73–8.61 | 4.22 | 1.80 | <0.05 | 1.83–9.74 |
| Dizygotic | Reference | – | – | – | Reference | – | – | – |
| Monozygotic | 5.88 | 2.50 | <0.001 | 2.55–13.53 | 4.21 | 1.22 | <0.001 | 2.38–7.43 |
| Male | Reference | – | – | – | Reference | – | – | – |
| Female | 0.72 | 0.42 | n.s. | 0.23–2.26 | 1.47 | 0.54 | n.s. | 0.72–3.00 |
| *Interaction Age of onset/female* | 3.46 | 2.98 | n.s. | 0.64–18.70 | 1.08 | 0.62 | n.s. | 0.35–3.30 |

Age at onset refers to the age at onset in the first diagnosed twin, while sex refers to the second twin.

within the first three intervals (<18, [18–22), [22–30)) all have an increased risk of schizophrenia (Table 4). In fact, having a diagnosed co-twin with onset below 18 years increases the risk of illness 7 times ([1.3–39]), likewise onset from 18 to 22 years increases the risk off illness 9 times ([2.8–30.9]). Results were similar for schizophrenia spectrum with a significantly increased risk of schizophrenia spectrum in the co-twin with lower age at onset of the diagnosed twin. Upon dividing the sample into four age intervals, the sample size was smaller and it was not possible to apply the same analysis strategy (with gender specific analysis and interaction terms) as in Table 2.

Kaplan-Meier curves documented a closer proximity in time of diagnoses among MZ twins than DZ twins following both the onset of schizophrenia and schizophrenia spectrum disorder in the co-twin (Fig. 2a; Chi2 = 15.12, $P < 0.001$, Fig. 2b; Chi2 = 16.55, $P < 0.001$).

## 4. Discussion

A key finding in this study is the almost five times increased risk of schizophrenia in the second twin when the first diagnosed twin was under the age of 22 at the first appearance of illness, with a more pronounced effect in female twins. Further division of the age at onset of schizophrenia spectrum disorders into four age intervals, led to a significant increase in illness risk in the second twin with decreasing age in the first diagnosed twin. Furthermore, we confirmed that the stronger genetic component in MZ twins than in DZ twins is manifested in the proximity of diagnosis within pairs. The key strength of this study is the inclusion of representative data from a nationwide twin cohort constituting the largest and most updated twin sample in schizophrenia research.

Our main finding indicates, that early illness onset can be perceived as a clinical marker for increased genetic vulnerability. This is in line with a study showing that increased family illness load predicted an earlier age at illness onset (Goldberg et al., 2011) and a Swedish register-based study investigating age-specific risk of illness with the highest risk found in the youngest age groups (Li et al., 2007). In our study the risk seemed more prominent in females, suggesting that early onset in females is caused by a higher genetic burden. This is consistent with females in general having a lower risk of developing schizophrenia than

**Table 3**
The sex-specific risk (hazard ratio (HR)) associated with developing schizophrenia ($N = 447$)/schizophrenia spectrum ($N = 787$) in the second twin, if the first twin had an illness onset before age 22 in a cohort of twins born 1951–2000 identified by linkage of Danish Twin Register and the Danish Psychiatric Central Research Register.

| | HR | Std. error | *P*-value | 95% CI | HR | Std. error | *P*-value | 95% CI |
|---|---|---|---|---|---|---|---|---|
| Females | Schizophrenia ($N = 215$) | | | | Schizophrenia spectrum ($N = 386$) | | | |
| Age of onset ≥ 22 | Reference | – | – | – | Reference | – | – | – |
| Age of onset < 22 | 8.66 | 5.24 | <0.001 | 2.65–28.33 | 4.66 | 1.75 | <0.001 | 2.23–9.72 |
| Dizygotic | Reference | – | – | – | Reference | – | – | – |
| Monozygotic | 5.26 | 3.23 | <0.01 | 1.58–17.51 | 4.15 | 1.70 | <0.05 | 1.86–0.26 |
| Males | Schizophrenia ($N = 232$) | | | | Schizophrenia spectrum ($N = 401$) | | | |
| Age of onset ≥ 22 | Reference | – | – | – | Reference | – | – | – |
| Age of onset < 22 | 2.53 | 1.59 | n.s. | 0.74–8.70 | 4.07 | 1.68 | <0.05 | 1.81–9.14 |
| Dizygotic | Reference | – | – | – | Reference | – | – | – |
| Monozygotic | 6.91 | 4.20 | <0.01 | 2.10–22.76 | 4.28 | 1.77 | <0.001 | 1.90–9.64 |

The hazard ratio (HR) associated with schizophrenia/schizophrenia spectrum in the second twin predicted by age at disease onset in the first diagnosed twin, adjusted for zygosity and sex of the second twin.

**Table 4**
The risk (hazard ratio (HR)) associated with developing schizophrenia/schizophrenia spectrum in the second twin, divided into intervals (<18, 18–22, 22–30, >30) regarding the age at onset in the first diagnosed twin (schizophrenia $N = 447$ pairs)/schizophrenia spectrum ($N = 787$ pairs), based on a national cohort of 31,524 twin pairs born 1951–2000 and identified by linkage of Danish Twin Register and the Danish Psychiatric Central Research Register.

| | Schizophrenia ($N = 447$) | | | | Schizophrenia spectrum ($N = 787$) | | | |
|---|---|---|---|---|---|---|---|---|
| | HR | Std. error | *P*-value | 95% CI | HR | Std. error | *P*-value | 95% CI |
| AAO ≥ 30 | Reference | – | – | – | Reference | – | – | – |
| AAO < 18 | 7.07 | 6.16 | <0.05 | [1.28–38.99] | 10.72 | 4.96 | <0.001 | [4.33–26.54] |
| AAO [18–22) | 9.25 | 5.70 | <0.001 | [2.76–30.94] | 6.06 | 2.40 | <0.001 | [2.79–13.15] |
| AAO [22–30) | 2.96 | 1.83 | n.s. | [0.88–9.94] | 2.72 | 1.02 | <0.01 | [1.30–5.66] |
| Gender | | | | | | | | |
| °Male | Reference | – | – | – | Reference | – | – | – |
| °Female | 1.44 | 0.61 | n.s. | [0.62–3.32] | 1.54 | 0.43 | n.s. | [0.89–2.65] |
| Dizygotic | Reference | – | – | – | Reference | – | – | – |
| Monozygotic | 5.83 | 2.48 | <0.001 | [2.54–13.40] | 4.18 | 1.21 | <0.001 | [2.37–7.35] |

males (Pedersen et al., 2014) and thereby may require a stronger genetic contribution to affect the predisposition to illness. Sex difference was not apparent for the broader illness category. The association of increased familial aggregation of schizophrenia with a younger age at onset was also described in a meta-analysis (Esterberg et al., 2010).This applied to both sexes; however but without familial aggregation males had a significantly earlier onset. The results further underline the importance of genetic factors to affect early illness onset in females, whereas an early onset for the male sex to a larger extent could be influenced by other risk factors, such as environmental risks. This is supported by evidence from a study showing that early onset cases are more likely to be males that have experienced obstetric complications and had a history of drug abuse and low academic performance (Liu et al., 2013), and from a study in male patients where accumulated environmental risks significantly lowered age at illness onset (Stepniak et al., 2014). In conclusion, these findings indicate that female sex may modify the association with early onset of schizophrenia and increase risk and supports a role for sex-specific genetic interactions. All though the findings are significant, a specific limitation is the low number of cases (concordant pairs) when dividing the dataset into both illness onset before and after age 22 and sex. Other studies support differences in illness presentation between males and females regarding premorbid adjustment and symptom severity but not to illness course (Goldberg et al., 2011; Drake et al., 2016). However, there is contradictory evidence for a specific genetic association to sex differences in schizophrenia (Hänninen et al., 2007; Yuan et al., 2013; Bergen et al., 2014; Chow et al., 2016). When dividing the age at onset in four intervals we were able to examine the possible presence of a more stepwise increase of risk rather than the dichotomous cut in before and after age 22. Here we found an increasing risk of illness in the second twin with decreasing age at onset in the first diagnosed twin (Table 4). In general the confidence intervals are rather wide, which reflect a small number of cases in each age group, especially when studying the narrow illness definition (Table 1). In the schizophrenia spectrum category where more cases are included, all results are significant and have smaller confidence intervals.

In this study we are unable to estimate the contribution of environmental factors to schizophrenia risk. We interpret the overall higher risk in MZ twins (in all our results) as indication of the importance of genetic factors according to the classical twin model (Boomsma et al., 2002). Furthermore, one assumption in the classical twin model is the "Equal Environment Assumption", i.e. that DZ twins share their environment to the same extend as MZ twins (Rijsdijk and Sham, 2002). This has been subject to debate, and if MZ twins do share a more equal

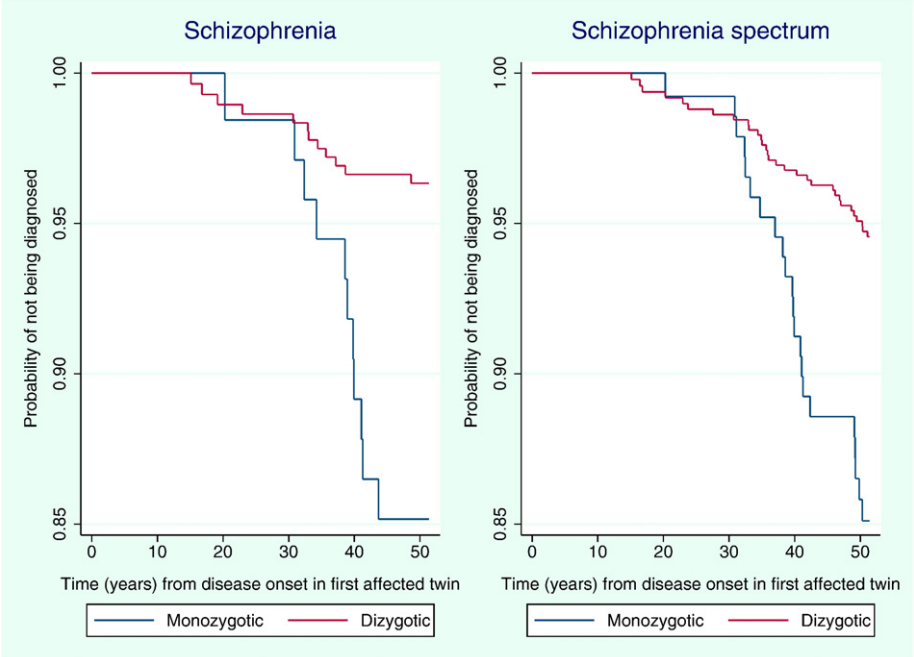


**Fig. 2.** Time difference between onset of diagnosis in affected twin pairs with schizophrenia (a; $N = 447$ twin pairs) and schizophrenia spectrum (b; $N = 787$ twin pairs) respectively, based on information from linkage of the Danish Twin Register and the Danish Psychiatric Central Research Register in a national cohort of twin pairs born 1951–2000.

environment than DZ twins, then the impact of genetic factors on illness risk can be overestimated. The observation of significant genetic effects does not insinuate that the environmental risks are less important because schizophrenia is a complex disorder with a heterogeneous clinical presentation (Owen et al., 2016). Indeed it is influenced by both genetic and several environmental risk factors and the complex interaction between them (Davis et al., 2016).

We showed that the almost identical genetic background in MZ twins compared with the average genetic identity of 50% in DZ twins is reflected in higher concordance with respect to time at illness onset within pairs, i.e. in MZ twins the observed time span between the assignments of the diagnoses is shorter than in DZ twins (Fig. 2). To our knowledge, the association of a shared genetic background and timing of illness onset in twins has not been demonstrated previously. A study of genetic influence on subtypes of schizophrenia, such as age at onset, did not show a simple genetic architecture in relation to early illness onset (Bergen et al., 2014), but our results indicate the importance of genetic effects in the pattern of illness onset in twin pairs. The Kaplan Meier curve in Fig. 2a and b does not stratify between the outcome and possible competing risks. Accordingly, the absolute figures on the Y-axis must be taken with reservation. The most important competing risk in this study is occurrence of death before having a possible diagnosis of schizophrenia spectrum. In this study, we can assume that censoring and competing risks will be the same for MZ and DZ twins, thus we expect the result of a greater proximity of schizophrenia spectrum disorders in MZ twins compared to DZ twins, to be governed by genetic effects rather than competing risks.

The Kaplan-Meier curves illustrating schizophrenia and schizophrenia spectrum are similar (Fig. 2a and b). This indicates that the timing of illness onset does not seem to differ when comparing a narrow illness definition to the broader including the schizophrenia spectrum. Also the HR estimated in Tables 1–3 does not indicate profound differences in the two diagnostic outcomes. In general, our results support that the genetic susceptibility covers a broad phenotypic outcome in the full spectrum of schizophrenia. Previous studies have also confirmed the importance of a broad approach when estimating the risk of severe mental illness in relatives (Mortensen et al., 2010; Rasic et al., 2014).

General strengths and limitations: The present sample consists of twin pairs from a comprehensive, nationwide register and is as such less liable to ascertainment bias. Removing twin pairs with UZ from the estimates might introduce a selection bias, but since the degree of shared genetic material is unknown in UZ twins, it is not possible to study genetic importance in risk of early illness onset. As a national register, the Danish Psychiatric Central Research Register is highly representative of patients with schizophrenia in Denmark since only a minimal number of patients are treated privately (Mors et al., 2011). Furthermore, a recent study demonstrated a high validity of the register diagnosis in schizophrenia consolidating the validity and consistency of the register diagnosis (Uggerby et al., 2013). Despite the comprehensive register data undiagnosed cases could exist. Additionally, the register-based data does not provide specific information on the twin pairs, thereby we are unable to include knowledge on environmental parameters of interest, such as whether twin pairs were reared together, or information on e.g. the importance of the prodromal phase, which could be relevant when addressing illness risk. In general, there may be a twin diagnosis bias in which there is a higher probability for the second twin to come to the attention of clinicians and thus be diagnosed, which could partly explain the increased risk of schizophrenia in the second twin. It is also possible that clinicians may be more attentive towards families presenting with an early onset case. The use of a Danish twin sample may limit the generalizability of our findings. In general it is assumed that twins are representative for the general population (Rijsdijk and Sham, 2002).

In conclusion, our examination of a large twin cohort indicates that age at illness onset might be perceived as a clinical marker for increased genetic vulnerability regarding schizophrenia spectrum. This is based on the significant association between increased illness risk and early age at illness onset. Furthermore, female cases with early illness onset may require an even stronger genetic contribution to express the illness phenotype, indicating sex as a potential modifier.

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## Declaration of Interests

None of the authors have any conflict of interest to declare.

## Contributors

RH and DH contributed equally and substantially to the conception and design of the study, data acquisition, analysis and interpretation of results, and drafting and revising the manuscript. BF, TW, MN and BG contributed to data acquisition, conception and design of the study, interpretation of results and critical review of the manuscript. AS and KC has contributed to data acquisition and critical review of the manuscript.

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